of time for submission of the Brief on Appeal is respectfully requested. A Petition for Extension of Time and the appropriate fee are being filed concurrently herewith. The Request for Continued Examination is being filed in lieu of the Brief on Appeal.

REMARKS

Rejection of Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 have been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification "does not reasonably provide enablement for embodiments wherein the first lentiviral nucleotide sequence does not comprise the gagpol sequences operatively linked to a RRE." Applicants respectfully disagree with this assessment.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. In re Borkowski, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). See also M.P.E.P. § 2164.02.

A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

The specification teaches packaging cell lines engineered to express lentivirus proteins, including HIV proteins, necessary for virus particle formation (gagpol proteins), without containing nucleic acid sequences from lentivirus or HIV accessory proteins (tat, vif, vpr, vpu, nef and rev proteins and RRE) or constitutive transport elements CTEs) (see, e.g., page 9, lines 17-21; and page 10, lines 13-17). The specification teaches that these cell lines can be produced using a first plasmid or retroviral nucleotide sequence (packaging construct) comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins (e.g.,

HIV *gagpol* proteins) but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs (see, e.g., page 4, lines 19-23; page 5, lines 4-8; page 9, line 17 to page 10, line 2; page 10, lines 13-22; page 11, lines 4-7; page 12, line 22 to page 13, line 2).

The specification teaches that packaging cell lines of the invention can be produced using a three plasmid expression system. In particular, the specification teaches that the packaging cell lines can be produced by co-transfecting mammalian host cells with (1) a first plasmid or retroviral nucleotide sequence (packaging construct) comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins (e.g., HIV *gagpol* proteins) but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs; (2) a second plasmid or retroviral nucleotide sequence (envelope coding plasmid) comprising a DNA sequence which encodes a heterologous envelope protein; and (3) a third plasmid or retroviral nucleotide sequence (transfer vector) comprising a DNA sequence of interest and lentivirus or HIV cis-acting sequences required for packaging, reverse transcription and integration (see, e.g., page 4, lines 19-27; page 5, lines 4-12; page 9, lines 17-21; page 10, lines 13-17; page 11, lines 4-7; page 11, lines 9-13; and page 12, line 22 to page 13, line 2).

The specification teaches that packaging cell lines of the invention can also be produced by co-transfecting mammalian host cells with (1) a first plasmid or retroviral nucleotide sequence (packaging construct) comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins (e.g., HIV *gagpol* proteins) but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs; and (2) a second plasmid or retroviral nucleotide sequence (envelope coding plasmid) comprising a DNA sequence which encodes a heterologous envelope protein (see, e.g., page 2, lines 13-19; page 3, lines 14-20; page 4, lines 23-27; page 5, lines 8-12; page 11, lines 4-9; and page 12, line 22 to page 13, line 2). The specification also teaches that packaging cell lines of the invention can be produced by co-transfecting mammalian host cells with (1) a first plasmid or retroviral nucleotide sequence (packaging construct) comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins (e.g., HIV *gagpol* proteins) but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs; and (2) a second plasmid or retroviral nucleotide sequence (transfer vector) comprising a DNA sequence of interest and lentivirus or HIV cis-acting sequences required for packaging, reverse transcription and integration (see, e.g., page 3, lines 1-8; page 4, lines 3-9; page 4, lines 23-27; page 5, lines 8-12; page 11, lines 4-7; page 11, lines 13-16; and page 12, line 22 to page 13, line 2).

The specification teaches that lentivirus-derived, including HIV-derived, retroviral particles having no viral accessory proteins can be generated using a three plasmid expression system. In particular, the specification teaches that lentivirus-derived, including HIV-derived, retroviral particles having no viral accessory proteins can be generated by co-transfecting mammalian host cells with (a) a packaging construct comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins (e.g., HIV *gagpol* proteins) but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs; (b) a envelope encoding plasmid comprising a DNA sequence which encodes a heterologous envelope protein; and (c) a transfer vector comprising a DNA sequence of interest and lentivirus or HIV cis-acting sequences required for packaging, reverse transcription and integration (see, e.g., page 16, line 5 to page 17, line 5).

Methods for constructing the plasmids and retroviral nucleotide sequences used to produce the packaging cell lines and lentivirus-derived and HIV-derived retroviral particles were readily available in the art at the time the subject application was filed.

The packaging construct provides the codon optimized lentivirus *gagpol* proteins or HIV *gagpol* proteins of the viral particles (see, e.g., page 12, line 22 to page 13, line 13). The envelope encoding plasmid provides a heterologous envelope protein which permits pseudotyping of viral particles generated by the packaging construct (see, e.g., page 14, lines 4-8). The transfer vector provides, *inter alia*, the lentivirus or HIV cis-acting sequences required for packaging, reverse transcription and integration of the viral particles (see, e.g., page 17, lines 12-16).

Thus, armed with the teachings in the specification and what was known to the skilled artisan at the time the subject application was filed, it would have been a routine matter for one skilled in the art to construct packaging cell lines comprising, *inter alia*, a plasmid or retroviral nucleotide sequence which comprises a codon optimized DNA sequence which encodes lentivirus or HIV *gagpol* proteins but not DNA sequences encoding lentivirus or HIV accessory proteins or CTEs. Armed with the teachings in the specification and what was known to the skilled artisan at the time the subject application was filed, it would have been a routine matter for one skilled in the art to generate lentivirus-derived or HIV-derived retroviral vector particles having no viral accessory proteins. Accordingly, Applicants submit that the guidance provided in the specification, coupled with what was known to the skilled artisan at the time the subject application, was filed is sufficient to enable the skilled artisan to make and use the full scope of

the claimed method without undue experimentation. No evidence to the contrary has been presented.

The Examiner questions that the teachings in the specification are sufficient to enable one skilled in the art to practice the claimed invention without undue experimentation because "the prior art teaches that the presence of some sort of transport element, either a Rev/RRE element or CTE, operatively linked to the gagpol coding sequences is essential for formation of recombinant viral particles in a minimal lentiviral system wherein most of the assessory proteins have been omitted." Paper No. 15, at page 6, lines 6-9. The Examiner points to Kim *et al.* (*J. Virology*, 72(1):811-816 (1998)) as providing evidence in support of his position, alleging that "[t]he major difference between the system claimed by applicants and that described [by Kim *et al.*] is that the gagpol sequence found on applicants' packaging vector has been codon-optimized for expression" and "[c]odon-optimization would not be expected to have any bearing on efficient transport of the nucleic acid comprising the optimized gagpol sequences". Paper No. 20, at page 4, lines 5-8. Applicants respectfully disagree with this assessment.

Kim *et al.* teach a three-plasmid expression system to generate HIV-1-derived retroviral vector particles by transient transfection of mammalian cells. This three-plasmid system features (a) a first plasmid comprising, *inter alia*, HIV sequences for packaging and mRNA export (referred to as a vector genome plasmid); (b) a second plasmid comprising *wildtype* coding sequences for HIV-1 gagpol and coding sequences for RRE or CTE; and (c) a third plasmid comprising the VSV-G gene (envelope protein). Kim *et al.* teach that their HIV-1-based vector production system lacks *tat*, *vif*, *vpr*, *vpu* and *nef* (Kim *et al.*, page 811, abstract; page 811, column 2, paragraph 2; and page 814, column 2, paragraph 3). Although Kim *et al.* teach that their HIV-1-based vector production system requires the rev/RRE accessory system (Kim *et al.*, page 814, column 2, paragraph 3), the reference does not question the use of Applicants' three plasmid system which comprises, *inter alia*, a packaging construct comprising a *codon optimized* coding sequence for lentivirus *gagpol* or HIV *gagpol* but not coding sequences for HIV accessory proteins or CTEs, to generate lentivirus-derived or HIV-derived retroviral vector particles having no viral accessory proteins (i.e., without Tat, Vif, Vpr, Vpu, Nef and Rev and RRE). Kim *et al.* also do not provide evidence that would lead one skilled in the art to the conclusion that Applicants' claimed invention is unbelievable. Accordingly, Kim *et al.* do not provide a sufficient basis to question the enablement provided in the subject specification for Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37.

Since the filing of the parent application, additional work has been done which demonstrates that packaging cell lines can be produced as described in the application by co-transfecting mammalian host cells with a plasmid or retroviral nucleotide sequence (packaging construct) comprising a codon optimized DNA sequence which encodes lentivirus *gagpol* proteins (e.g., HIV *gagpol* proteins) but not DNA sequences encoding lentivirus or HIV accessory proteins (tat, vif, vpr, vpu, nef and rev proteins and RRE) or constitutive transport elements (CTEs). The additional work is described in the Declaration of John T. Gray, Ph.D. under 37 C.F.R. § 1.132 filed concurrently herewith. The results described in the Declaration demonstrate that packaging cell lines expressing HIV *gagpol* gene products can be produced without the addition of viral sequences encoding lentivirus or HIV accessory proteins (tat, vif, vpr, vpu, nef and rev proteins and RRE) or CTEs, as described in the application.

The results presented in the Declaration also demonstrate that, contrary to the Examiner's allegation, codon optimization does have a bearing on expression of HIV *gagpol* gene products, particularly enabling high level expression of HIV *gagpol* in the absence of viral sequences encoding lentivirus or HIV accessory proteins (tat, vif, vpr, vpu, nef and rev proteins and RRE) or CTEs.

Additionally, the Kotsopoulou *et al.* reference (*J. Virol.*, 74(10):4839-4852 (2000); attached hereto as the Exhibit), an article published after the effective filing date of the subject application, also describes results which demonstrate that codon optimization of the HIV-1 *gagpol* gene leads to higher expression of gagpol gene products without the requirement for Rev/RRE (i.e., expression is Rev independent). Kotsopoulou *et al.* also report the use of their codon optimized HIV *gagpol* gene to construct HIV vectors lacking all of the accessory proteins (Kotsopoulou *et al.*, page 4839, abstract; and page 4850, column 1, last paragraph). Accordingly, Kotsopoulou *et al.* provide further evidence that one skilled in the art would find that the guidance provided in the specification, coupled with what was known to the skilled artisan at the time the subject application was filed, is sufficient to enable the skilled artisan to make and use the full scope of the claimed method without undue experimentation.

Reconsideration and withdrawal of the rejection of Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that

a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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